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# THE TAMILNADU Dr.M.G.R MEDICAL UNIVERSITY

# CHENNAI -600032.

# A STUDY OF PROFILE OF METASTATIC BRAIN TUMOURS

**Dissertation submitted in partial fulfillment of M.Ch BRANCH II (NEUROSURGERY) -3YEARS EXAMINATION AUGUST 2011**

**INSTITUTE OF NEUROLOGY**

**MADRAS MEDICAL COLLEGE**

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# CERTIFICATE

This is to certify that **Dr.K.MADHUSUTHAN** has been a post graduate student during the period from August 2008 to August 2011 in the Department of Neurosurgery, Institute of Neurology, Madras Medical College, Government General Hospital, Chennai.

This dissertation titled **"A STUDY OF PROFILE OF METASTATIC BRAIN TUMOURS "** is a bonafide work done by him during the study period and is being submitted to the Tamil Nadu Dr.M.G.R Medical University in partial fulfillment of the M.Ch BRANCH II – 3 year course, neurosurgery examination.

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# DECLARATION

I, Dr.K.Madhusuthan, solemnly declare that the dissertation titled **“ A STUDY OF PROFILE OF METASTATIC BRAINTUMOURS”** has been prepared by me and is submitted to the Tamilnadu Dr.M.G.R Medical University in partial fulfillmentof rules and regulations for the M.Ch degree examination

Place : Chennai

Date : Dr.K.Madhusuthan.

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# CONTENTS

# INTRODUCTION

Metastatic brain tumors are one of the common intracranial neoplasms encountered in Neurosurgical practice. 8-10% of adults with cancer will develop symptomatic metastases during life[5.] About 20% of patients with systemic malignancy develop cerebral metastases when patients survives upto one to two years. Most cases of brain metastases remain unreported. Majority of brain metastasis arise from one of the two common sites: lung cancer and breast cancer[21,33].The frequency of metastatic brain tumors is increasing because of superior imaging modalities and earlier detection and treatment and also longer survival after primary cancer diagnosis because of more effective treatment of systemic disease[14]. Still the number of reported cases in India is only the tip of iceberg, of the actual incidence of metatases in brain.

Appropriate management of patients with brain metastases requires an assessment of independent prognostic factors in order to maximize survival and neurological function while avoiding unnecessary treatments.

There is no comprehensive study in Indian population regarding the behavior of brain metastases and various prognostic factors. Although the reported cases of cerebral metastasis are only a small percentage of the actual incidence in

the society, this Institution being a tertiary referral centre and has both Neurosurgery department and Radiation oncology department , studying the incidence and other epidemiological factors may closely reflect the actual situation in the society. So in this study an attempt has been made to study the behavior, distribution and various factors affecting the survival in patients with brain metastases.

Moreover in this study ,the previously studied variables like Karnofsky performance status ,age , number of metastases, systemic disease activity, source of primary, time between primary onset to brain metastases as individual prognostic factors were analyzed and also many new factors like edema in imaging appearance, treatment modality and their impact on survival were also studied.

# LITERATURE REVIEW

Brain metastases are one of the common intracranial space occupying lesions. With the increasing survival of patients with systemic disease, the incidence of the most brain metastases from common cancers (lung, breast, melanoma, renal and colon) is thought to be rising. Autopsy data show that the frequency of brain metastases in patients dying from cancer varies from 20 to 50%, and may be higher if dural, leptomeningeal, or spinal metastases are taken into account[14] .The most common source of brain metastases in males is lung cancer and in females is breast cancer[14, 24] .

## INCIDENCE

Metastatic brain tumors account for about 24-45% of all cancer patients[5]. The incidence of metastatic brain tumors exceeds that of primary brain tumors, accounting for 50% of total brain tumors and for as many as 30% of tumors seen on imaging studies alone .The prevalence of brain metastasis is thought to be 120,000-140,000 per year in US[5]. This disease accounts for 20% of cancer deaths annually[4.]

About 60% of patients with metastatic brain tumors are aged 50-70 years. More than 20% of patients with systemic disease have brain metastasis on

autopsy. About 15% of patients with cancer present with neurologic symptoms before their systemic cancer is diagnosed[25,27] . Among them, 43-60% have an abnormal chest radiograph suggestive of bronchogenic primary or other metastases to the lung. In 9%, the CNS is the only site of spread. About 10% of patients with proven metastatic disease have no identifiable primary source [5].

## SOURCE OF PRIMARY

The most common origins of brain metastases are systemic cancer of the lung, breast, skin, or GI tract. In the study conducted by Barnholtz .et al ,the distribution of primary cancer was as follows: 48% lung, 15% breast, 9% melanoma, 1% lymphoma (mainly non-Hodgkin), 3% GI (3% colon and 2% pancreatic), 11% genitourinary (21% kidney, 46% testes, 5% cervix, 5% ovary), 10% osteosarcoma, 5% neuroblastoma, and 6% head and neck tumor [5].

Primary lung tumors account for 50% of all metastatic brain tumors. Lung cancer is the most common origin of metastatic disease. Of lung cancer patients who survive for more than 2 years, 80% will have brain metastases[20,24] .

The average time interval between the diagnosis of primary lung cancer and brain metastases is 4 months. Interestingly, small cell carcinomas, which are only 20% of all lung cancers, account for 50% of brain metastases from lung cancer[22]..

Breast tumor is the main source of metastatic disease in women, followed by melanoma, renal, and colorectal tumors [5]. The interval between the diagnosis of primary breast cancer and brain metastasis can be up to 3 years. HER positive cancer is twice as common to metastasize to the brain. Additionally, it has been shown that nm23 and CD44 in breast cancer are indicators for distant metastasis.

Melanoma commonly metastasizes to the brain. Melanoma has an increased incidence among other systemic cancers in terms of metastasizing to the brain. About 40-60% of patients with melanoma will have brain metastasis. Melanoma cells are closely related to CNS cells due to their embryonic origin and neural crest cells, and they share common antigens such as MAG-1 and MAG-2. Approximately 14% of cases have no identifiable primary tumor [33].

## SINGLE/MULTIPLE :

Metastatic disease from the breast, thyroid, renal cells, and colon are more commonly found as a single metastatic lesion, whereas metastatic disease from lung cancer , melanoma and cancers of unknown primary are more commonly found to be multiple lesions[21,31].

## INTRACRANIAL SITE OF METASTASES :

Both the left side and the right side of the brain were equally represented (right 48%, left 46%, and center 6%). The frontal, parietal, and temporo-parieto-occipital regions were more often involved than the temporal and occipital lobes[11]. Among patients with a single metastasis from a primary tumor situated in the pelvis (prostate or uterus) and abdomen (gastrointestinaltract), the incidence of infratentorial metastases was 50% , compared with 10% in patients with other primary tumors [1,11]. There is a preferential location of metastasis in the posterior border zone (between the middle and posterior cerebral arteries) and in the anterior border zone (between the anterior and middle cerebral arteries).

## PATHOLOGY :

Most brain metastases result from arterial tumoral microemboli , in agreement with the rule that emboli tend to pass along the arterial tree as far distally as the size permits. During transient episodes of increased abdominal pressure with compression of the vena cava, tumor could seed the spine directly, without transiting through the lungs. The cerebral dural sinuses are a direct extension of the spinal epidural plexus [26]. The pathway is through the basilar plexus of veins to, in part, the inferior petrosal sinuses, which are an important outlet for the cerebellum

and brain stem. Metastases via this retrograde pathway could provide an explanation for the preferential involvement of the posterior fossa in patients with abdominal and pelvic primary tumors[27].

## SEX

Although melanoma spreads to the brain more commonly in males than in females, gender does not affect the overall incidence of brain metastases[5,20] .

## AGE

About 60% of patients are aged 50-70 years. CNS metastasis is not common in children; it accounts for only 6% of CNS tumors in children. Leukemia accounts for most metastatic CNS lesions in young patients, followed by lymphoma, osteogenic sarcoma, and rhabdomyosarcoma.

## SYNCHRONOUS/METACHRONOUS DISEASE :

Patients with brain metastasis at the same time of having systemic cancer (synchronous metastasis) tend to do worse as compared with patients with metachronous metastatic disease[25] .

## PATHOPHYSIOLOGY OF METASTATIC DISEASE

To metastasize, tumor cells have to gain access to the circulation, survive while circulating, pass through the microvasculature of the adopted organs, extravasate into the organ parenchyma, and reestablish themselves at the secondary site. The tumor cells penetrate the basement membrane and cross the subendothelial membrane by producing proteolytic enzymes like metalloproteinases and cathepsins. Tumor cells also modulate the expression of fibronectin, collagen, or laminin, and change the type of integrin receptor on their surface and on the surface of the surrounding stromal cells, resulting in desegregation of the stromal cells and creating a permissive environment for them to expand and invade.

Invading cells detach from the tumor mass, disperse, and traverse the epithelial/endothelial boundary. Tumor cells have to survive intravascular circulation and avoid immune surveillance during this journey by coating themselves with a shield made out of the coagulating elements such as fibrin and platelets in the blood. These metastatic emboli also produce adherens to slow themselves down to a halt in the blood stream. These adheren molecules allow the circulating cancer cells to reattach onto the vascular wall and gain entry to the host tissue by disruption of the endothelial barrier. This leads to re-establishment of

distant micrometastasis[26]. When a tumor increases in volume by more than 2-3 times, the tumor expresses angiogenic factors such as angiopoietin-2 and vascular endothelial growth factors. These angiogenic modulators promote sprouting of surrounding blood vessels, which results in tumor angiogenesis[18,26] .

Different tumors metastasize preferentially to different organs. Cells with similar embryologic origins are generally believed to have similar growth constraints and express similar sets of adhesion molecules, such as addressins. An example is melanoma; the cells are closely related to CNS cells (they are derived from the neural crest cells), and melanoma commonly metastasizes to the brain. Certain cell-surface markers in cancer are indicators and/or predictors of distant metastasis, eg, nm23 and CD44 in breast cancer. Similarly, breast cancer cells that are HER positive are more likely to metastasis to the brain[26]. Renal, gastrointestinal, and pelvic cancer tend to metastasize to the cerebellum, whereas breast cancer is more commonly found in the posterior pituitary[33]. Thus, the trafficking of cancer cells to their final destination is not entirely random and may be guided by factors produced by stromal cells of their host organ .

The mechanisms by which primary tumors produce brain metastases is thought to be hematogenous spread from primary or secondary sites in the lung.

Since the brain has no lymphatic system, all tumors metastasizing to the brain do so by spreading through the bloodstream. Arterial blood passes through the lungs before entering the brain, and collects tumor cells filtered out in capillaries, which subsequently embolize to the brain. This is correlated with sites of localization: the cerebrum is involved in 80 to 85% of all brain metastases, the cerebellum in 10 to 15% and the brainstem in 3 to 5% . The overall distribution corresponds roughly to the relative size of blood flow regions in the brain[26,33] .

## CLINICAL FEATURES:

Approximately 60% of patients with brain metastases have subacute symptoms[18]. Acute onset of symptoms suggests vascular or electrical etiology such as bleeding or seizure. Paraneoplastic syndromes include limbic encephalopathy and cerebellar degeneration. The latter is commonly associated with ovarian cancer. Progressive weight loss and general fatigue can be ominous and highly suggestive of recurrent systemic cancer. Headache (42%) and seizure (21%) are the 2 most common presenting symptoms[14]. The other common symptoms are cognitive dysfunction(35%) and 30% have motor dysfunction.

## Physical findings

Focal findings are common. Findings consistent with generalized CNS dysfunction also can occur secondary to the cumulative effects of multiple CNS lesions and edema associated with large single or multiple CNS lesions[18] .

## BRAIN METASTASES IMAGING

Magnetic resonance imaging (MRI) with contrast enhancement is the procedure of choice, because MRI is more sensitive and specific than other imaging modalities in determining the presence, location, and number of metastases [1,11]. Contrast-enhanced computed tomography (CT) scanning is used widely because of easy accessibility and low cost[31]. Numerous studies have shown that contrast-enhanced MRI detects 2-3 times as many lesions as contrast-enhanced CT, especially lesions less than 5 mm in diameter. Approximately 20% of patients with solitary metastatic lesions on CT show multiple lesions on MRI [1].

CT BRAIN:

Metastases frequently are multiple; they are seen at the junction of gray and white matter, usually with significant surrounding edema. On noncontrast CT, the density of metastatic lesions may be less than, equal to, or greater than that of adjacent brain parenchyma. Most of the patterns are variable and are

nondiagnostic. IV administration of contrast material (30-40 g iodine) increases the diagnostic accuracy of CT. Most metastases enhance after a standard dose of IV contrast. Use of a higher dose of contrast (80-85 g of iodine) and delaying scanning by 1-3 hours after injection of the contrast agent lead to a further increase in the detection of multiple metastases. In cases involving a solitary metastatic lesion of the brain, detection of an additional lesion may have a bearing on treatment; with multiple lesions, surgical treatment may be forgone in favor of chemotherapy or radiation therapy [31] .

CT brain has a sensitivity of 92%, a specificity of 99%, and an accuracy of 98% in detecting brain metastases. Mostly, the lesions missed on contrast-enhanced CT were smaller (<2 cm in diameter) and were located next to the bone in a frontotemporal location. Dural-based metastases may mimic meningioma.

MRI BRAIN:

Lesions are isointense to mildly hypointense on T1-weighted images; they are hyperintense on T2-weighted images or with fluid attenuation inversion recovery.Surrounding edema is relatively hypointense on fluid attenuation inversion recovery and on T1-weighted images; they are hyperintense on T2-weighted images[11].

Hemorrhagic metastases or melanoma lesions are hyperintense on T1-weighted images. On T2-weighted images, mucinous adenocarcinoma may be hypointense, owing to calcification; hemorrhagic metastases may be hypointense, owing to the chronic breakdown of blood products. Following administration of a contrast agent, solid, nodular, or irregular ring patterns of enhancement are seen. Nonenhancing lesions are less likely to be metastases[24].

PET SCAN:

With 18-fluorodeoxyglucose (FDG) positron emission tomography (PET) , intracerebral metastases may appear as areas of increased metabolism. Radionuclide studies are sensitive but are highly nonspecific. Currently, FDG-PET is not considered superior to CT or MRI in the initial evaluation of suspected brain metastases[11]. Radionuclide imaging was reported to detect intracerebral metastases in approximately 90% of patients, but the findings were nonspecific. Neoplasm, inflammation, vascularity, or trauma may cause the abnormal uptake. FDG-PET has been reported to detect approximately two thirds of brain metastases resulting from systemic cancer.

ANGIOGRAPHY:

Angiography currently is not used as a primary diagnostic procedure for metastatic disease. Preoperative angiography and embolization of large hypervascular metastases from renal and thyroid cancer may be useful. The value of angiography is nonspecific in the diagnosis of metastases[24] .

## TREATMENT OF BRAIN METASTASIS

Current treatment options include whole-brain radiation therapy (WBRT), surgical resection, stereotactic radiosurgery , and chemotherapy. Corticosteroids and antiepileptic medications are commonly used for palliation of mass effect and seizures.

## WBRT

WBRT is the primary choice for the majority of patients with brain metastases. WBRT for brain metastases was first described 50 years ago by Chao et al . The RTOG has evaluated a number of different radiation fractionation schemes, but median survival seems independent of the dose and schedule[2,9] . WBRT is given in either 10 fractions of 3 Gy over 2 weeks (30 Gy) or 15 fractions of 2.5 Gy each to a total dose of 37.5 Gy. Accelerated hyper-fractionated regimens delivering up to 70.4 Gy focal radiation offer no additional benefit

relative to the conventional schedule[19] . WBRT reduces symptoms and improves or stabilizes overall and neurocognitive function; however, survival with this treatment modality alone is poor, and control of brain metastases is achieved in only half of patients.

Daily fractions >3 Gy likely increase the risk for neurotoxicity. In clinical practice, WBRT is commonly delivered to patients with multiple brain metastases not amenable to surgery or SRS, poor functional status, or active or disseminated systemic disease with effective palliation of neurological symptoms[32].

SIDE EFFECTS : Significant neurotoxicity has been reported with the use of WBRT. Acute effects include hair loss (alopecia), nausea, vomiting, lethargy, otitis media and severe cerebral edema. Though some of these effects can be transient, dermatitis, alopecia, and otitis media can persist for months after irradiation . Chronic effects are even more serious, and these include atrophy, leukoencephalopathy, radiation necrosis, neurological deterioration and dementia. Reports of development of severe radiation induced dementia have varied between 11% in one-year survivors to 50% in those surviving two years[2,12] .

The use of adjuvant WBRT following resection or radiosurgery has also been proved to be effective in terms of improving local control of brain metastases and

thus decreasing the likelihood of neurologic death. Approximately 70% of patients with brain metastases experience relapse after resection, if WBRT is omitted[19].

The best evidence from the currently available trials suggests that optimal radiation treatment of brain metastases consists of a multimodal approach involving a combination of surgery or radiosurgery with WBRT in patients stratified by RPA class. In many cases, the addition of WBRT represents a conservative approach that can improve local control and delay intracranial recurrence[19] .

Withholding WBRT increases intracranial failure and neurologic deterioration is more directly related to disease progression in the brain[19] . In the recent phase III trial of WBRT with or without motexafin gadolinium, the most significant predictor for neurologic and neurocognitive decline, as well as deterioration in quality of life, was disease progression in the brain[34] .

## WBRT PLUS CHEMOTHERAPY

Several chemotherapeutic agents have been studied in combination with WBRT for patients with brain metastases, including chloroethylnitrosoureas, tegafur, fotemustine, and teniposide. Although most have shown higher response rates in the experimental arm, all have been at the expense of greater toxicity with

no benefit in overall survival. The combination of WBRT and low-dose (75 $mg/m^2$) daily temozolomide (TMZ) has shown promising response rates with acceptable toxicity in patients with newly diagnosed brain metastases from a variety of solid tumors[6].

Various studies have shown a significantly higher neurological progression-free survival rate in the TMZ arm .Several studies have shown promising tolerability and response rates for concurrent TMZ and WBRT, particularly for non-small cell lung cancer (NSCLC) and melanoma, but current data do not support the widespread use of the combination in patients with new brain metastases. A future treatment strategy may be to assess tumor $O^6$-methylguanine–DNA methyltransferase methylation status as a way of preselecting a group of patients with a greater likelihood of responding to TMZ.

## Prophylactic cranial irradiation:

In patients with small cell lung cancer (SCLC), who have a ≥50% estimated 2-year risk for central nervous system (CNS) relapse, PCI reduces the risk for brain metastases by 50% and increases overall survival by 16%–18% in patients with a clinical response to chemotherapy based on a meta-analysis of 12

randomized trials. PCI has also been investigated in high-risk NSCLC patients, and there is currently insufficient evidence to support its use in this population[32] .

## SURGERY:

Less than 50% of patients with metastatic disease have a single tumor and only about 50% of these patients have surgically accessible tumors[8] . The remainder of patients have many tumors or deeply-situated deposits which increases the surgical complexity[6] .Surgery is an important modality for patients with a single brain metastasis, particularly when favorable prognostic factors and systemic disease control are present. Surgery significantly reduced brain metastasis recurrence and prolonged median survival . Patients treated with surgery and WBRT have significantly longer median survival than those who received WBRT alone[20] .

In many studies the surgery plus WBRT arm had a longer median survival time (9.2 months versus 3.4 months), higher local control rate (80% versus 48%), longer duration of functional independence, defined as a KPS score ≥70 (38 weeks versus 8 weeks), and longer freedom from death resulting from neurological causes compared with patients treated with WBRT and biopsy alone[20]. In patients with multiple metastases, surgery is usually limited to patients with a dominant,

symptomatic, or life-threatening lesion and/or those who require a tissue diagnosis before proceeding with therapy. Recent single-center retrospective studies suggest that patients with good prognostic features and two to three metastases may gain similar survival benefit from surgery when the dominant lesion is resected[13] .

The combination of surgical resection followed by WBRT is a more effective treatment for control of metastatic brain disease compared with surgery or radiotherapy alone[20].RPA class 1 patients have median survival times essentially double those of patients in RPA class 2 or class 3 when treated with surgery plus postoperative WBRT.

The complication of surgery are wound infection, pseudomeningocoele formation and thromboembolic complications such as deep vein thrombosis or pulmonary embolisms and an operative mortality of approximately 3% [8] .

## RADIOSURGERY

Radiosurgery refers to the delivery of a single large dose of radiation to a small intracranial target, using a stereotactic localization system, and maximal head immobilization, frequently achieved by using a minimally invasive stereotactic head frame. This precise system allows optimal targeting of tumor regions while maximally and conformally avoiding healthy brain tissue[10]. SRS

employs multiple convergent beams to deliver a single, large dose of radiation to a discrete target volume. The three most common delivery systems are the linear accelerator, gamma knife, and cyclotron, which make use of high-energy photons, gamma rays, and protons, respectively. Maximum-tolerated doses of 15, 18, and 24 Gy have been established by the RTOG 90–05 protocol for tumors 31–40 mm, 21–30 mm, and ≤20 mm in maximum diameter, respectively[10].

SRS does not address distant failure in the brain. Complications from SRS include early treatment-induced edema, reported in 4%–6% of patients within 1–2 weeks of treatment ; seizures within the first 24–48 hours, reported in 2%–6%]; and delayed radiation necrosis, reported in 2%–17%. The risk for radiation necrosis increases with larger tumor volume, higher radiation dose, and prior radiotherapy[35]. Combined WBRT plus radiosurgery boost significantly improves control of metastatic brain disease in patients with two to four brain metastases[10].

## Chemotherapy

Chemotherapy has traditionally played a limited role in the treatment of brain metastases and has been reserved for patients who have failed other treatment modalities or for diseases known to be "chemosensitive," such as lymphoma, SCLC, germ-cell tumors, and, to a lesser degree, breast cancer[6] .

Temozolomide is a recently developed second-generation oral alkylating prodrug that is converted to an active metabolite, 5-(3-methyltriazen-1yl)imidazole-4-carboximide, and has nearly 100% bioavailability. Temozolomide readily crosses the blood-brain barrier, producing cerebrospinal fluid concentrations that are ~30% of plasma concentrations. There is some synergy with radiation[6,34] .Toxicity to temozolomide is general low, with <5% of patients experiencing myelosuppression. Temozolomide has shown activity in patients with recurrent or newly diagnosed brain metastases from various malignancies. The response rate was 24% for non–small-cell lung cancer, 19% for breast cancer, and 40% for melanoma[6]. Thus, temozolomide and radiation therapy may have promise in patients with brain metastases, especially for those with lung cancer and melanoma.

Lapatinib a novel targeted drug that can be administered orally and inhibits the tyrosine kinase of ErbB1 (epidermal growth factor receptor) and ErbB2 (HER2) receptors. Similarly gefitinib, an ErbB1 (epidermal growth factor receptor) inhibitor, prove efficacious in the treatment of brain metastases[6].Approximately one third of women with HER2-positive metastatic breast cancer will eventually develop CNS metastases. Lapatinib is under investigation, both as a single agent and in combination with trastuzumab, in women with metastatic breast cancer[34,35] .

**NSCLC**

Several chemotherapeutic regimens have modest activity against NSCLC. Cisplatin (CDDP) has activity both as a single agent and in combination in patients with brain metastases from NSCLC. Response rates of 30% for single-agent CDDP and 28%–45% for CDDP in combination with paclitaxel and other agents like vinorelbine , gemcitabine, etoposide have been reported[13] .

Vascular endothelial growth factor pathway inhibitors such as bevacizumab and small-molecule receptor tyrosine kinase inhibitors such as sorafenib and sunitinib have shown activity in NSCLC and may potentially be useful for brain metastases either alone or in combination but all are entering clinical trials only presently[34] .

**Breast cancer**

Objective response rates in the range of 43%–59% have been reported in patients with new brain metastases from breast cancer treated with cyclophosphamide in combination with 5-fluorouracil (5-FU) and prednisone. These regimens may be considered either before or after WBRT in patients with newly metastatic breast cancer to brain who have not yet received cyclophosphamide-based chemotherapy, particularly in the presence of active

systemic disease[9]. In the recurrent setting, TMZ is the best studied because of its favorable BBB penetration, ease of administration, and low toxicity profile. Better systemic disease control and survival in patients treated with trastuzumab , and poor BBB penetration of trastuzumab, which may provide a "sanctuary site" for brain tumor growth while systemic disease is controlled . In these patients the dual EGFR and HER-2 tyrosine kinase inhibitor lapatinib has showed modest activity in a recent phase II study [15] .

## SURVIVAL AND PROGNOSIS OF METASTATIC DISEASE

Appropriate management of patients with brain metastases requires an assessment of independent prognostic factors in order to maximize survival and neurologic function whilst avoiding unnecessary treatments. Important variables include: age, performance status (most commonly designated by the Karnofsky performance status [KPS] score, number of brain metastases (single or multiple), primary tumor type (lymphoma, germ cell, and breast versus other), and systemic tumor activity (controlled versus uncontrolled). Of these, the KPS score has consistently been shown to be the major determinant of survival, secondary only to treatment regimen in most studies[4] . Time from primary tumor diagnosis to

development of brain metastases holds prognostic value as well, particularly for breast and melanoma primaries, with long intervals being favorable [15,25].

A three-tiered prognostic categorization was derived from 1,200 patients in the Radiation Therapy Oncology Group (RTOG) database using recursive partitioning analysis (RPA).

The overall survival duration for patients in RPA class 1, defined as those with a KPS score ≥70, age <65 years, controlled primary tumor, and no extracranial sites of disease, was 7.1 months. The median survival duration was only 2.3 months for patients in RPA class 3, defined as all patients with a KPS score <70. The median survival duration for the remainder, RPA class 2, was 4.2 months [15,16].

**KARNOFSKY PERFORMANCE STATUS:**

**Table 1.** Karnofsky performance status (KPS) scale

| Score | Clinical characteristics |
|---|---|
| 100 | Normal, no complaints, no evidence of disease |
| 90 | Able to carry on normal activity; minor symptoms of disease |
| 80 | Normal activity with effort; some symptoms of disease |
| 70 | Cares for self; unable to carry on normal activity or work |
| 60 | Requires occasional assistance but is able to care for needs |
| 50 | Requires considerable assistance and frequent medical care |
| 40 | Disabled; requires special care and assistance |
| 30 | Severely disabled; hospitalization is indicated, death not imminent |
| 20 | Very sick, hospitalization necessary; active treatment necessary |
| 10 | Moribund, fatal processes progressing rapidly |
| 0 | Dead |

# AIM OF STUDY

This study aims at analyzing the incidence of metastatic brain tumours , their distribution, the source of primary, the imaging characteristics, their site preference, the various treatment modalities and factors affecting the survival and outcome.

# MATERIALS AND METHODS

**MATERIALS** : All metastatic brain tumour patients reporting to The Institute of Neurology and The Department of Radiation Oncology from August 2008 to January 2011 were included in the study. These patients belong to one of the following groups

1. Patients with biopsy proven primary disease presenting with imaging evidence of intracerebral metastasis.
2. Patients with biopsy proven intracerebral metastasis with known primary.
3. Patients with biopsy proven intracerebral metastasis with no known source of primary

**Patient exclusion criteria :**

All patients with neither the primary nor the secondary proven by biopsy were excluded from the study.

A total of 102 patients qualified for the study.

**OBJECTIVE : The following factors were studied like**

1. Incidence and Age & sex distribution

2. Source of primary according to age and sex

3. Imaging characteristics of metastatic brain tumours with respect to primary.

4. Clinical features of metastatic brain tumours.

5. Number of metastatic brain tumours and its relevance to source of primary and survival.

6. Karnofsky performance status of the patients with metastatic brain tumours and its relevance to survival.

7. To analyze and predict the overall survival with relevance to age ,KPS, source of primary , presence of systemic disease , time interval between primary and secondary .

8. Various treatment options like surgery, WBRT, chemotherapy and their effect on prognosis.

9. Average survival with relevance to primary patholollgy and karnofsky performance status.

**Type of study:**

It is a prospective study and a descriptive study.

**Follow up period :**

The follow up period ranged from 1week to 2 years, with an average of 24 weeks.

A detailed proforma (Appendix-1) incorporating all the relevant aspects of the study was formulated and recorded for each and every patient separately. The entire datas were incorporated into a master chart(Appendix-2) and it was analyzed by multivariate analysis using SPSS software and chi-square test .

## RESULTS :

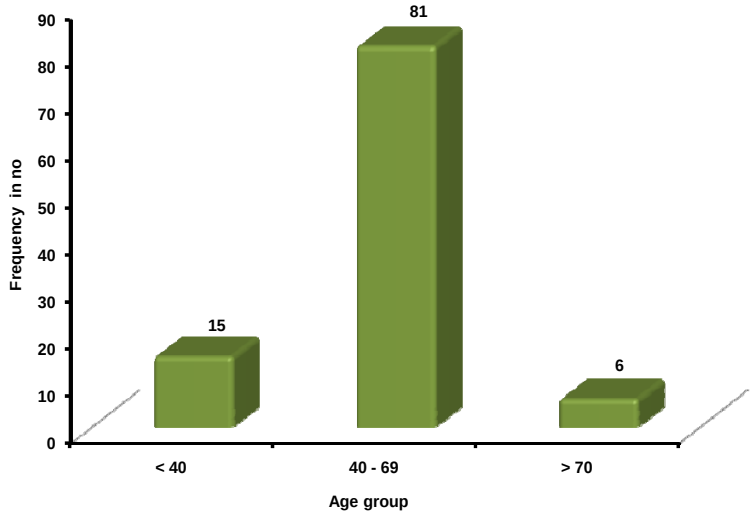
There were 102 cases of metastatic brain tumours which fulfilled the inclusion and exclusion criteria and they were studied during the period from August 2008 to January 2011. Out of the 102 cases, 90 cases were under regular follow up.12 cases were lost to follow up during the study period. The follow up percentage is 88.2%.

**AGE DISTRIBUTION:**

TABLE-1-AGE DISTRIBUTION

| Age distribution | No | Percentage |
|---|---|---|
| < 40 | 15 | 14.7% |
| 40 – 69 | 81 | 79.4% |
| > 70 | 6 | 5.9% |

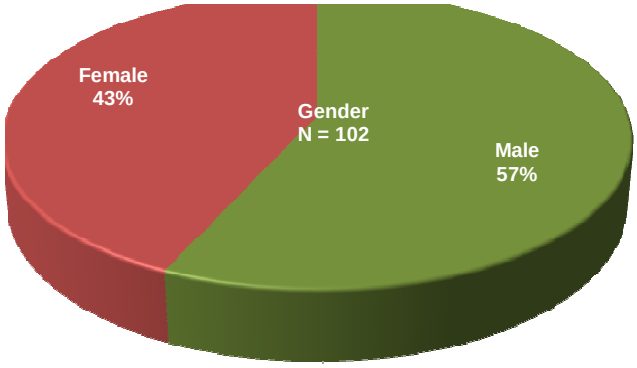
## CHART-1-AGE DISTRIBUTION




The youngest person in the study were two 17 year old persons, one with Hodgkin's disease and one with soft tissue sarcoma . The oldest person was aged 80 years and he was a case of bronchioalveolar carcinoma lung with brain metastases. There were 15 patients in less than 40 age group (14.7%) and 81 patients in 40 to 69 age group (79.4%) and 6 patients in above 69 age group (5.9%). Majority of metastatic brain tumours were in the age group 40 to 69.

## SEX :

### CHART-2 – SEX DISTRIBUTION




### TABLE-2-SEX DISTRIBUTION

| age | male | female | Ratio M:F |
|---|---|---|---|
| <40 | 3 | 12 | 1:4 |
| 40–69 | 43 | 38 | 1.13:1 |
| >69 | 4 | 2 | 2:1 |
| total | 54 | 48 | 1.12:1 |

There were 54 male and 48 female patients with a male:female ratio of 1.12:1. There were more females than males in the less than 40 age group with male:female ratio 1:4. Whereas in more than 40 age, there was not major difference between incidence in males and females.

## CLINICAL FEATURES:

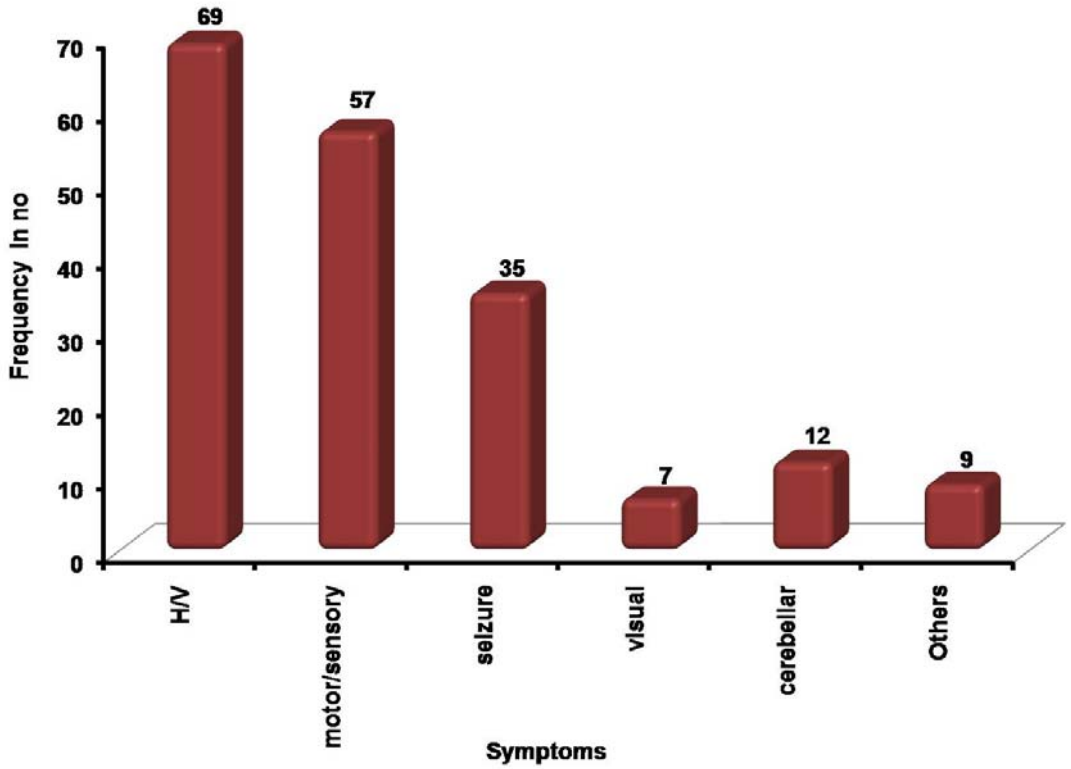
The average symptom duration before presentation is 10.4 weeks, with some cases presenting within a week to some cases presenting as delayed as one year. The common clinical presentation is headache in 69(67.6%), motor complaints in 57(55.9%), seizures in 35(34.3%), visual complaints in 7 (6.9%) cases, cerebellar features in 12(11.8%) cases. Headache is the most common symptom followed by motor deficit and seizures in that order.

Clinical evidence of Cerebellar involvement was present in only 46% cases with radiological evidence of cerebellar involvement. The clinical presentation depends on the location of intracerebral metastasis. The other clinical features (8.8%) include memory disturbances, speech disturbances, disturbed orientation and lower cranial nerve palsy.

## TABLE -3 CLINICAL FEATURES

| Symptoms | NO | Percentage |
|---|---|---|
| H/V | 69 | 67.6% |
| motor/sensory | 57 | 55.9% |
| Seizure | 35 | 34.3% |
| Visual | 7 | 6.9% |
| Cerebellar | 12 | 11.8% |
| Others | 9 | 8.8% |

## CHART-3–CLINICAL FEATURES



**NUMBER OF METASTASES :**

Out of the 102 cases 49 were single metastasis and 53 multiple metastases. Out of the 49 cases with single metastasis, 44 were under follow up with 14 alive(30%) and 31(70%) dead**.** In the multiple metastasis group 46 of the 53 cases were under follow up with 12 alive (26%) and 34 dead(73%). In lung primary, metastasis was single in 23 cases and multiple in 20 cases and in breast primary , 8 cases had single metastasis and 7 cases had multiple metastasis. Similarly in unknown primary, 9 cases had single metastasis and 14 cases had multiple metastases.

The distribution of single and multiple metastases among various primary groups is given in the Table-5. In this study the incidence of single and multiple metastasis is almost similar overall (49:53) and also in lung and breast primary. In unknown primary, multiple metastases is common than single metastasis(60.8%). In other disease groups, the total number of cases is small to conclude their preference for single or multiple metastases. Presence of single or multiple metastases was not affecting the outcome independently.

CHART-4- NUMBER OF METASTASES

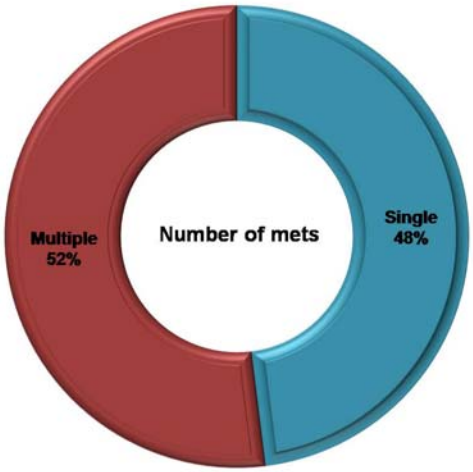



CHART-5-DISTRIBUTION OF NUMBER OF METASTASES

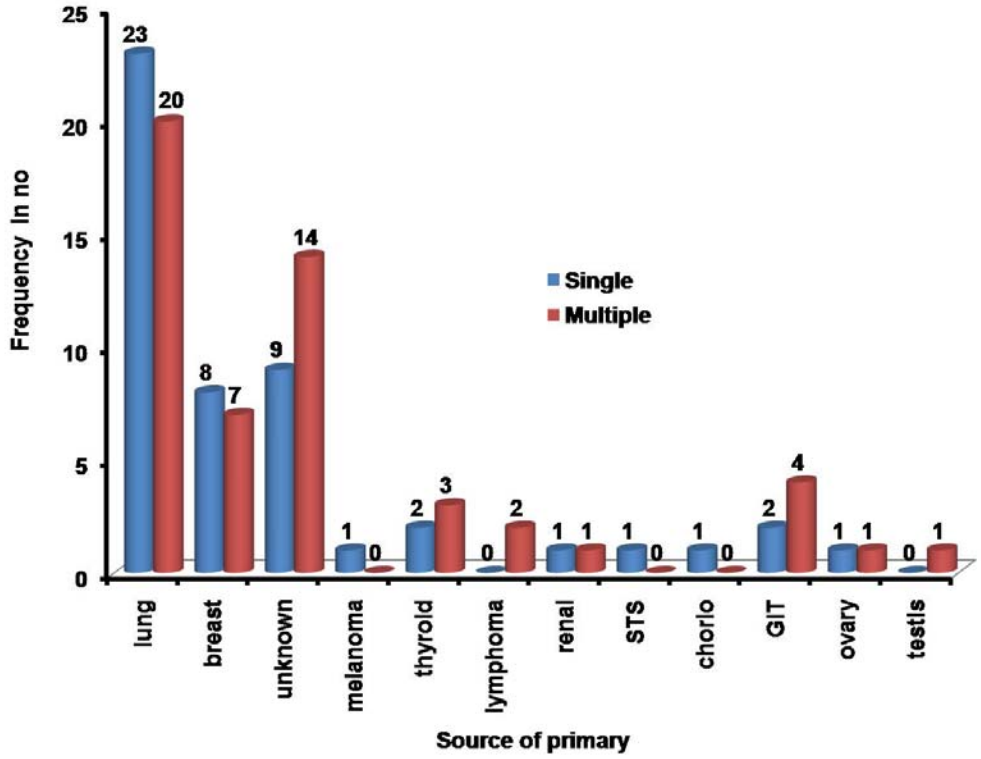


TABLE -4 NUMBER OF METASTASIS

| TOTAL | SINGLE | MULTIPLE |
|---|---|---|
| 102 | 49 | 53 |

TABLE-5 DISTRIBUTION OF METASTASIS

| **Source of primary** | **Number of mets** | |
|---|---|---|
| | **Single** | **Multiple** |
| Lung | 23 | 20 |
| Breast | 8 | 7 |
| Unknown | 9 | 14 |
| Melanoma | 1 | 0 |
| Thyroid | 2 | 3 |
| Lymphoma | 0 | 2 |
| Renal | 1 | 1 |
| STS | 1 | 0 |
| Chorio | 1 | 0 |
| GIT | 2 | 4 |
| Ovary | 1 | 1 |
| Testis | 0 | 1 |

## SOURCE OF PRIMARY:

CHART-6.SOURCE OF METASTASES

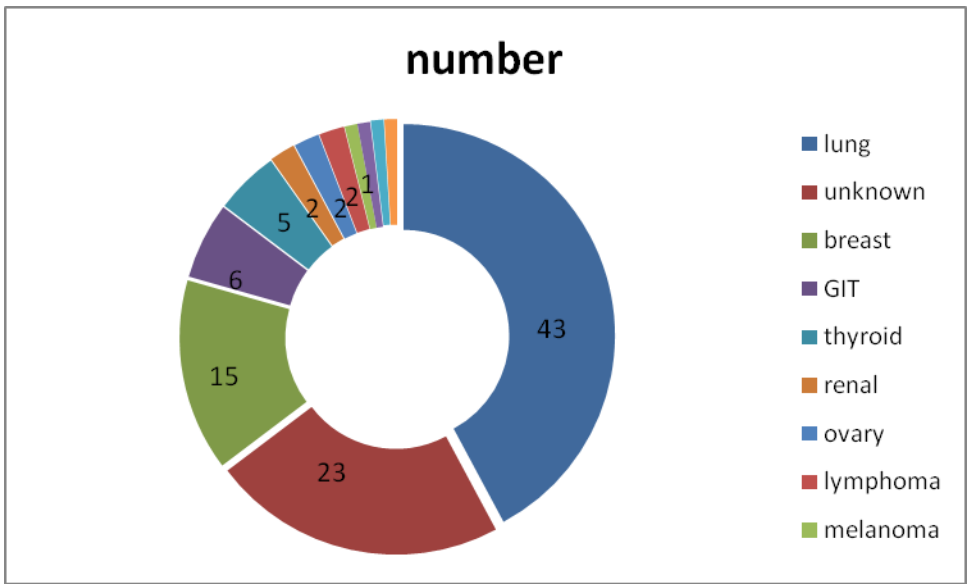



CHART-7.AGE GROUPAND SOURCE OF METASTASES

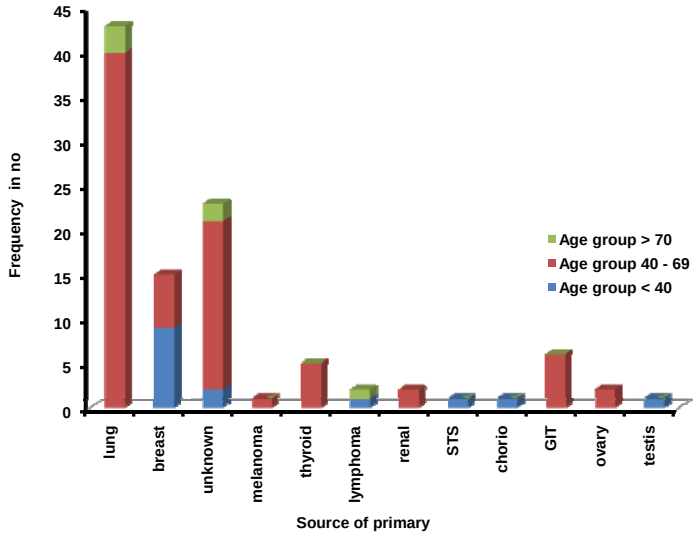


TABLE-6. SOURCE OF METASTASES

| Source of metastasis | Age group | | | |
|---|---|---|---|---|
| | < 40 | 40 - 69 | >70 | total |
| Lung | 0 | 40 | 3 | 43 |
| breast | 9 | 6 | 0 | 15 |
| unknown | 2 | 19 | 2 | 23 |
| melanoma | 0 | 1 | 0 | 1 |
| thyroid | 0 | 5 | 0 | 5 |
| lymphoma | 1 | 0 | 1 | 2 |
| Renal | 0 | 2 | 0 | 2 |
| STS | 1 | 0 | 0 | 1 |
| chorio | 1 | 0 | 0 | 1 |
| GIT | 0 | 6 | 0 | 6 |
| Ovary | 0 | 2 | 0 | 2 |
| Testis | 1 | 0 | 0 | 1 |

The most common source of primary is lung cancer(43), followed by unknown primary(23) and breast cancer(15) (Table6/Chart6). Lung is the most common source of primary (42%) overall and also in both sexes. It is the most common primary in all age groups except less than 40 where breast is the common primary. There were 43 lung primary, with no cases in less than 40 age group. Out of the 15 cases with breast primary, 9 cases(60%) were below 40 years group and 6

cases (40%) were in 40-69 age group. In unknown primary, 82.6% cases were in the age group 40-69 and 2 cases were each in below 40 years and greater than 69 years.

Among lung primary, 17 cases were small cell carcinoma, 10 cases of bronchioalveolar carcinoma, 7 cases of adenocarcinoma, 5 cases of squamous cell carcinoma and 4 cases of non small cell CA lung. All cases of breast carcinoma were infiltrating ductal carcinoma.

## IMAGING APPEARANCE

The imaging features of all patients were studied. MRI was done only in patients who could afford. Ring lesion is the common appearance of metastasis with 51 cases appearing as ring enhancing lesions(50%) (Picture-1). Metastasis had cystic appearance in 8 cases(Picture-2) and hemorrhagic appearance in 3 cases (Picture-3). In patients with cystic metastasis 3 cases each were from lung primary(6.9%) and unknown primary(13%) and 1 each from breast (6.6%)and renal primary(50%). There were 3 cases with hemorrhagic lesion one each from lung(NSCC), melanoma and choriocarcinoma.

TABLE-7.IMAGING APPEARANCE OF METASTASES

| Source of primary | Cyst | Hemo | Ring | contrast enhancement - Homo | contrast enhancement - Intense |
|---|---|---|---|---|---|
| lung | 3 | 1 | 24 | 7 | 9 |
| breast | 1 | 0 | 9 | 3 | 4 |
| unknown | 3 | 0 | 10 | 1 | 5 |
| melanoma | 0 | 1 | 0 | 0 | 1 |
| thyroid | 0 | 0 | 2 | 1 | 0 |
| lymphoma | 0 | 0 | 0 | 1 | 1 |
| renal | 1 | 0 | 0 | 0 | 0 |
| STS | 0 | 0 | 1 | 0 | 0 |
| chorio | 0 | 1 | 0 | 1 | 1 |
| GIT | 0 | 0 | 2 | 1 | 1 |
| ovary | 0 | 0 | 2 | 0 | 0 |
| testis | 0 | 0 | 1 | 0 | 0 |
| total | 8 | 3 | 51 | 15 | 22 |

Most of the cases showed heterogenous contrast enhancement, while only 15 cases (14.7%) showed homogenous intense contrast enhancement (Picture-4). Disproportionate edema (severe edema) was found in 14 cases and minimal to no edema in 14 cases. Remainder of the cases excibited mild to moderate edema. In

metastatic disease with breast primary, 10 of the 15 cases had no to mild edema(66%), whereas with lung and unknown primary edema factor was variable. Edema was very minimal in the two lymphoma cases studied. The imaging characteristics of various primaries and the edema component is distributed as shown in Table-7/Table-8 . Edema in imaging is also not specific to any source of primary(Chart-8).

CHART-8.EDEMA IN IMAGING

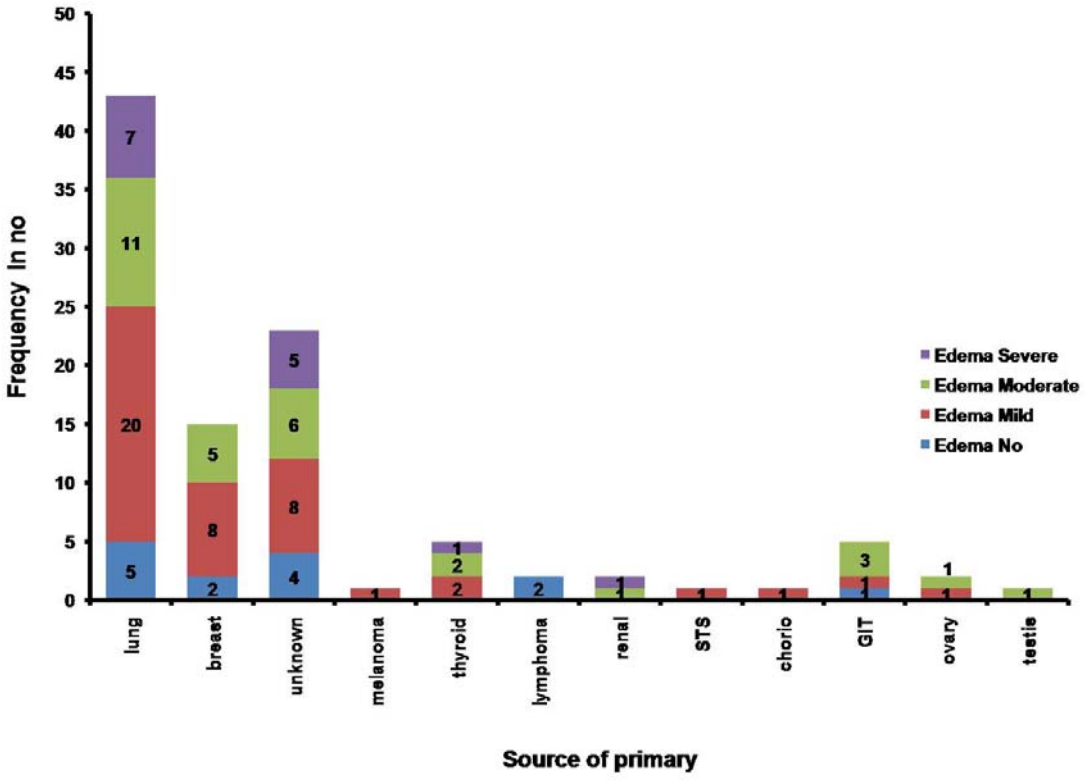


TABLE-8. EDEMA IN IMAGING

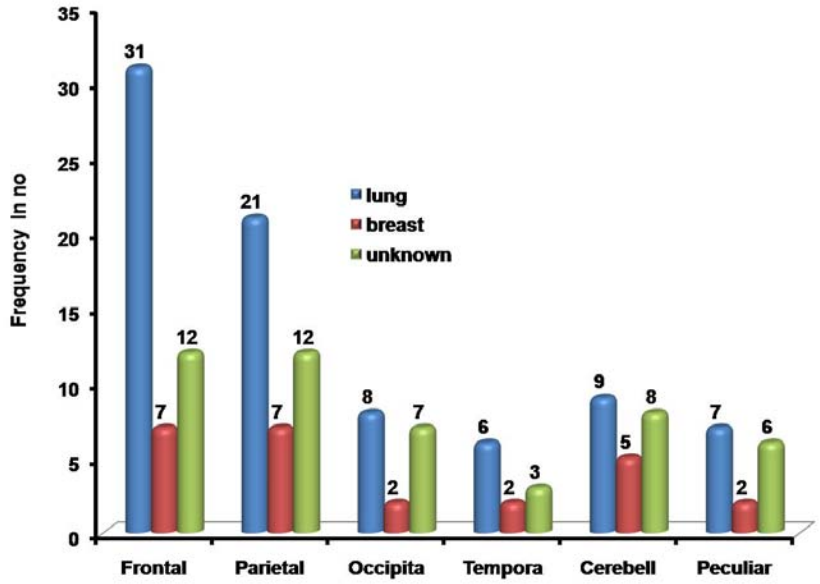
| Source of primary | Edema | | | |
|---|---|---|---|---|
| | No | Mild | Moderate | Severe |
| lung | 5 | 20 | 11 | 7 |
| breast | 2 | 8 | 5 | 0 |
| unknown | 4 | 8 | 6 | 5 |
| melanoma | 0 | 1 | 0 | 0 |
| thyroid | 0 | 2 | 2 | 1 |
| lymphoma | 2 | 0 | 0 | 0 |
| renal | 0 | 0 | 1 | 1 |
| STS | 0 | 1 | 0 | 0 |
| chorio | 0 | 1 | 0 | 0 |
| GIT | 1 | 1 | 4 | 0 |
| ovary | 0 | 1 | 1 | 0 |
| testis | 0 | 0 | 1 | 0 |
| total | 14 | 43 | 31 | 14 |

## SITE OF METASTASES:

Frontal lobe was involved in 66 cases (64%), parietal lobe in 47 cases (46%), occipital lobe in 22 cases(21%), temporal lobe in 18 cases (17.6%),

cerebellum in 26 cases (25%)and other location like internal capsule(3), basal ganglia(8), thalamus(3), brainstem(1) in total 18 cases(Table-9/Chart-9).

CHART-9. SITE OF METASTASES




The right hemisphere was involved in 37cases, left hemisphere in 30 cases and bilateral hemispheric involvement in 37 cases. Posterior fossa was involved in 33% of breast primary and 39% of unknown primary and in 20.5% of lung primary.

The most common location is frontal followed by parietal, cerebellum, occipital and temporal. The hemispheric involvement was almost similar with equal cases involving right and left hemisphere. In this study renal, GIT, pelvic

cancer metastasize to cerebellum in 45%, but the total number of the above primaries are less to be statistically significant.

TABLE-9.SITE OF METASTASES

| **Source of primary** | **Frontal** | **Parietal** | **Occipita** | **Tempora** | **Cerebell** | **Peculiar** |
|---|---|---|---|---|---|---|
| Lung | 31 | 21 | 8 | 6 | 9 | 7 |
| Breast | 7 | 7 | 2 | 2 | 5 | 2 |
| Unknown | 12 | 12 | 7 | 3 | 8 | 6 |
| Melanoma | 1 | 0 | 0 | 0 | 0 | 0 |
| Thyroid | 4 | 2 | 1 | 1 | 0 | 1 |
| Lymphoma | 2 | 1 | 0 | 1 | 0 | 0 |
| Renal | 0 | 1 | 0 | 0 | 1 | 1 |
| STS | 0 | 0 | 1 | 0 | 0 | 0 |
| Choriocarcinoma | 1 | 0 | 0 | 0 | 0 | 0 |
| GIT | 5 | 2 | 1 | 4 | 2 | 1 |
| Ovary | 2 | 0 | 0 | 0 | 1 | 0 |
| Testis | 1 | 1 | 1 | 0 | 0 | 0 |
| Total | 66 | 47 | 21 | 17 | 26 | 18 |

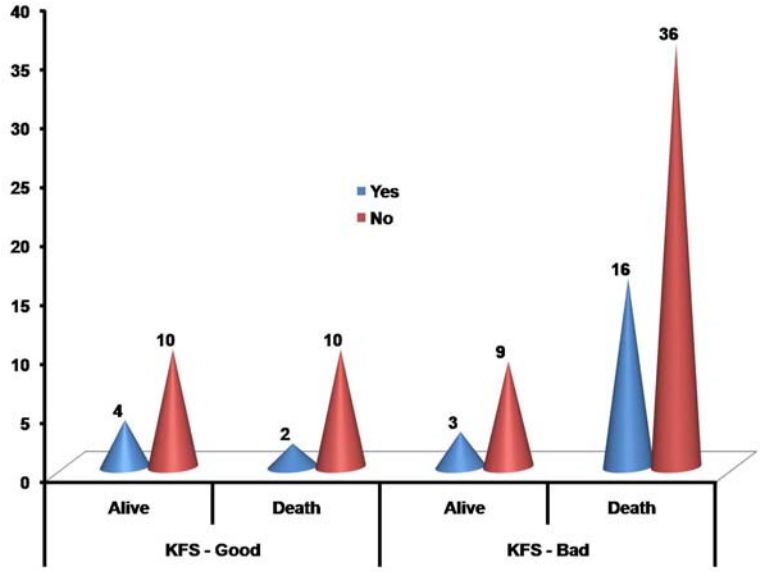
## FACTORS AFFECTING SURVIVAL

## SYSTEMIC DISEASE:

TABLE-10. SYSTEMIC DISEASE & SURVIVAL

| Systemic disease | KPS – Good | | KPS - Bad | | P-value |
|---|---|---|---|---|---|
| | Alive | Death | Alive | Death | |
| Yes | 4 | 2 | 3 | 16 | 0.838 |
| No | 10 | 10 | 9 | 36 | |

CHART-10. SYSTEMIC DISEASE



The presence of systemic tumour activity other than intracerebral metastasis, as evidenced by imaging was present in 29 cases , no systemic tumour activity in 73 cases. In patients with systemic tumour activity, 25 cases were under follow up with 7 cases alive (28%). In patients without systemic tumour activity, 65 cases were under follow up with 19 alive (29%). There was not difference in both the groups in terms of survival. Presence or absence of systemic tumour activity at presentation is not significantly associated with performance status and it was not an independent factor for survioval (Table-10/Chart-10)

**SOURCE OF METASTASIS**

In this study, breast primary had a survival rate of 58.3% (Table-11) . When breast primary is correlated with performance status, it is not significantly associated in predicting overall survival(Table-12) and survival at 3months and at 6months. Breast primary patients irrespective of their performance status had a 100% 3months and 6 months survival rate (Table-13).

Lung primary had a survival rate of 24.3% (Table-11). When lung primary is correlated with performance status, it is not significantly associated in predicting overall survival (Table-12) and survival at 3 months and 6 months(Table-14).

Unknown primary had a 23.8% survival rate (Table-11). Perforamance status significantly predicts overall survival (Table-12) and survival at 3months and 6months in metastatic disease with unknown primary(Table15).There were 2 cases of lymphoma with both of them alive during the study period (survival rate of 100%) . Patients with GIT primary had a survival rate of 40%, but the total number in these groups is less, to be statistically significant.The average survival in weeks for lung, breast, unknown primary are 21, 52.6 and 28 weeks respectively.

TABLE -11. DISEASE SPECIFIC SURVIVAL

| Source of primary | Alive | Death | Percentage alive |
|---|---|---|---|
| lung | 9 | 28 | 24.3% |
| breast | 7 | 5 | 58.3% |
| unknown | 5 | 16 | 23.8% |
| melanoma | 0 | 1 | - |
| thyroid | 1 | 4 | 20% |
| lymphoma | 2 | 0 | 100% |
| renal | 0 | 2 | - |
| STS | 0 | 1 | - |
| chorio | 0 | 1 | - |
| GIT | 2 | 3 | 40% |
| ovary | 0 | 2 | - |
| testis | 0 | 1 | - |
| | 26 | 64 | 28.8% |

## TABLE-12. SOURCE OF PRIMARY AND SURVIVAL

| Source of primary | KPS - Good | | KPS - Bad | | P-value |
|---|---|---|---|---|---|
| | Alive | Death | Alive | Death | |
| lung | 4 | 5 | 5 | 23 | 0.106 |
| breast | 5 | 1 | 2 | 4 | 0.079 |
| unknown | 3 | 2 | 2 | 14 | 0.030 |

## TABLE-13. BREAST PRIMARY AND SURVIVAL AT 3MONTHS/6MONTHS

| | 3months | |
|---|---|---|
| breast | total | alive |
| goodKPS | 6 | 6 |
| badKPS | 5 | 5 |

| | 6months | |
|---|---|---|
| breast | total | alive |
| goodKPS | 6 | 6 |
| badKPS | 4 | 4 |

## TABLE-14. LUNG PRIMARY AND SURVIVAL AT 3MONTHS/6MONTHS

| | 3months | | |
|---|---|---|---|
| lung | total | dead | P-value |
| goodKPS | 9 | 1 | 0.216 |
| badKPS | 28 | 9 | |

| | 6months | | |
|---|---|---|---|
| lung | total | dead | P-value |
| goodKPS | 6 | 2 | 0.272 |
| badKPS | 24 | 14 | |

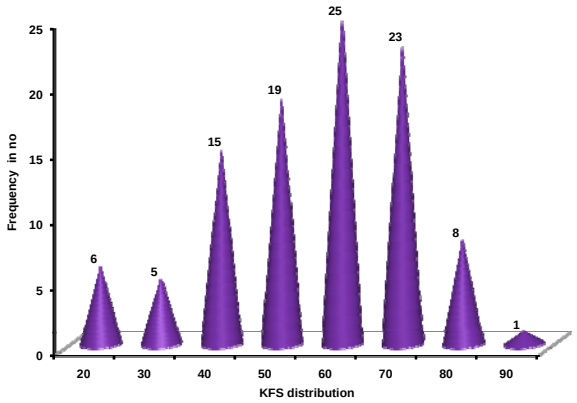
TABLE-15. UNKNOWN PRIMARY AND SURVIVAL AT 3MONTHS/6MONTHS

| | 3months | | | | 6months | | | |
|---|---|---|---|---|---|---|---|---|
| unknown | total | Alive | P-value | | unknown | total | alive | P-value |
| goodKPS | 5 | 5 | 0.015 | | GoodKPS | 5 | 5 | 0.002 |
| badKPS | 16 | 6 | | | badKPS | 14 | 3 | |

**PERFORMANCE STATUS:**

Performance status is determined by the Karnofsky's performance score. Patients were given a a score between 10 -100. In this study patients had a performance score between 20 to 90. Patients with performance score 70 and above were grouped as good score and 60 and below as bad score. In this study there were 32 patients with KFS score of 70 and above and 70 patients with karnofsky's score 60 and below. The total patients in each group is described in the Table-16 & Chart-11. About 25 cases had a performance score of 60, 23 cases had a performance score of 70 and 19 cases had a performance score of 19. Together these three performance scores accounted to 65 % of cases.

## CHART-11. PERFORMANCE STATUS DISTRIBUTION




## TABLE -16 . PERFORMANCE STATUS DISTRIBUTION

| KPS | NO |
|---|---|
| 20 | 6 |
| 30 | 5 |
| 40 | 15 |
| 50 | 19 |
| 60 | 25 |
| 70 | 23 |
| 80 | 8 |
| 90 | 1 |

The total patients alive in each Karnofsky score is given in Table-18 & Chart -12. The average survival in weeks in each KPS score is given below in Table-17

TABLE-17. KARNOFSKY & SURVIVAL DURATION

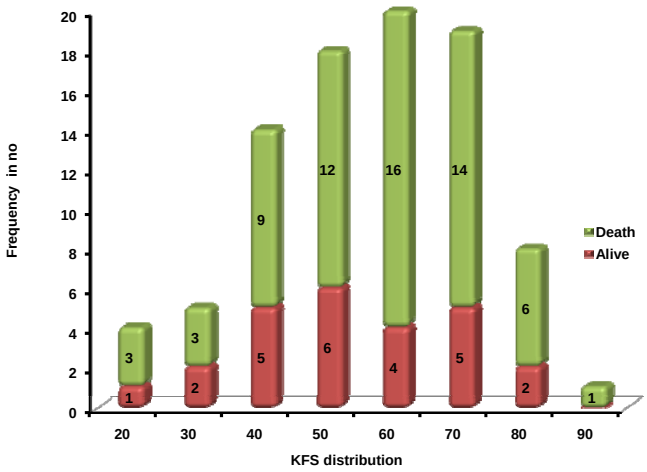
| KPS | Survival in weeks |
|---|---|
| 20 | 2.5 |
| 30 | 6.8 |
| 40 | 9 |
| 50 | 21.8 |
| 60 | 23.3 |
| 70 | 30.2 |
| 80 | 30.40 |
| 90 | 104 |

Survival duration is directly dependant on the performance score. Most of the patients had KPS of either 60 or 70. There was only one patient with performance score 90.

## TABLE 18.PERFORMANCE STATUS AND SURVIVAL

| KFS | Alive | Death |
|---|---|---|
| 20 | 1 | 3 |
| 30 | 2 | 3 |
| 40 | 5 | 9 |
| 50 | 6 | 12 |
| 60 | 4 | 16 |
| 70 | 5 | 14 |
| 80 | 2 | 6 |
| 90 | 0 | 1 |

## CHART -12. PERFORMANCE STATUS AND SURVIVAL



The Karnofsky performance status did not predict survival overall (Table-19). This is because the follow up duration varied between patients in the same Karnofsky score. But the performance score independently and significantly predicted survival at 3months , 6months and 1 year. (Table-20).

TABLE-19-PERFORMANCE STATUS AND SURVIVAL SIGNIFICANCE

| kfs | alive | dead | p value |
|---|---|---|---|
| good | 7 | 21 | 0.66 |
| bad | 18 | 43 | |

TABLE-20-PERFORMANCE STATUS AND SURVIVAL AT 3 MONTHS,6MONTHS & 1 YEAR

| | 3months | | p-value | | 6months | | pvalue |
|---|---|---|---|---|---|---|---|
| kfs | alive | dead | | kfs | alive | dead | |
| good | 25 | 1 | 0.001 | good | 20 | 2 | 0.000 |
| bad | 38 | 25 | | bad | 23 | 32 | |

| | 1year | | pvalue |
|---|---|---|---|
| kfs | alive | dead | |
| good | 10 | 8 | 0.000 |
| bad | 6 | 45 | |

**TREATMENT ;**

Patients were treated with either WBRT alone, or craniotomy with WBRT, or Stereotactic biopsy with WBRT, or craniotomy alone. Patients were chosen for

treatment as per guidelines. As Stereotactic radiosurgery is not available, it was not used as a treatment modality. There were 7 persons in whom craniotomy and excision alone was performed ,because patients refused RT or patients expired in the post operative period. Craniotomy and excision of lesion combined with WBRT was administered in 26 cases. WBRT alone was administered in 59 cases and stereotactic biopsy combined with WBRT in 8 cases. In the WBRT alone group consists of cases where the primary was proven by biopsy or anyother site of metastasis was proven by biopsy. Chemotherapy was administered in metastatic brain tumours with breast, small cell lung, GIT, lymphoma and ovarian primary.

Performance score was not significantly associated with treatment modality in predicting overall survival, except in patients treated with WBRT alone group(Table-21). The survival of patients with bad performance score was increased when craniotomy is combined with WBRT than craniotomy alone . But this association is not statistically significant. Similarly the survival of patients in bad performance score, treated with WBRT combined with craniotomy was better compared with WBRT alone (Table-22) and it was statistically significant. Treatment modality was not determining the outcome in patients with good performance status.

TABLE-21-TREATMENT MODALITY AND SURVIVAL

| | | KFS-good | | KFS-bad | | |
|---|---|---|---|---|---|---|
| treatment | no | alive | Dead | alive | dead | pvalue |
| Craniotomy alone | 7 | 0 | 0 | 1 | 6 | 0.198 |
| Craniotomy+WBRT | 26 | 4 | 3 | 7 | 12 | 0.353 |
| WBRT alone | 59 | 9 | 7 | 4 | 28 | 0.000 |
| Stereotactic BX+ WBRT | 8 | 1 | 2 | 0 | 4 | 0.212 |

TABLE-22-COMPARISON OF TREATMENT MODALITIES

| Bad kfs | alive | Dead | P-value | Bad kfs | alive | dead | P-value |
|---|---|---|---|---|---|---|---|
| Craniotomy | 1 | 6 | 0.198 | Cr+WBRT | 7 | 12 | 0.0476 |
| Cr+WBRT | 7 | 12 | | WBRT | 4 | 28 | |

**AGE AND SURVIVAL**:

Performance status was significantly predicting survival in the 40-69 age group (Table-23) . In less than 40 and greater than 69 age group , performance status was not predicting survival overall and also at 3 months , 6months and 1 year(Table-24& Table-25). Less than 40 was associated with a better survival than the greater than 70 age group.

## TABLE-23- AGE AND SURVIVAL

| Age distribution | KFS – Good | | KFS - Bad | | p-value |
|---|---|---|---|---|---|
| | Alive | Death | Alive | Death | |
| < 40 | 5 | 3 | 1 | 3 | 0.221 |
| 40 – 69 | 9 | 8 | 9 | 46 | 0.002 |
| > 70 | 0 | 1 | 2 | 3 | 0.439 |
| Total | 14 | 12 | 12 | 52 | |

## TABLE-24. AGE AND SURVIVAL AT 3MONTHS

| | 3months | | |
|---|---|---|---|
| <40 | total | alive | P-value |
| goodkfs | 8 | 8 | 0.087 |
| badkfs | 3 | 2 | |

| | 3months | | |
|---|---|---|---|
| >70 | total | dead | P-value |
| goodkfs | 1 | 1 | 0.273 |
| badkfs | 5 | 2 | |

## TABLE-25.AGE AND SURVIVAL AT 6MONTHS&1YEAR

| | 1year | | |
|---|---|---|---|
| <40 | total | alive | P-value |
| goodkfs | 6 | 4 | 0.673 |
| badkfs | 2 | 1 | |

| | 1year | | |
|---|---|---|---|
| >70 | total | dead | P-value |
| goodkfs | 1 | 1 | - |
| badkfs | 3 | 3 | |

| | | 6months | | |
|---|---|---|---|---|
| age | alive | dead | | pvalue |
| <40 | 9 | | 1 | 0.357 |
| goodkfs | 8 | | 0 | |

| | | 1year | | |
|---|---|---|---|---|
| age | alive | dead | | pvalue |
| <40 | 9 | | 1 | 0.326 |
| badkfs | 2 | | 1 | |

| | | 6months | | |
|---|---|---|---|---|
| age | alive | dead | | pvalue |
| >70 | 2 | | 3 | 0.809 |
| goodkfs | 1 | | 1 | |

| | | 1year | | |
|---|---|---|---|---|
| age | alive | dead | | pvalue |
| >70 | 2 | | 3 | 0.764 |
| badkfs | 2 | | 2 | |

## TABLE-26.NUMBER OF METASTASIS AND SURVIVAL

| NUMBER | good kfs alive | dead | bad kfs alive | dead | | |
|---|---|---|---|---|---|---|
| single | 5 | 8 | 9 | 22 | Pvalue- | 0.54 |
| multiple | 10 | 4 | 4 | 30 | Pvalue- | 0.00 |
| | P-value | 0.76 | P-value | 0.58 | | |

## TABLE-27.NUMBER OF METASTASIS AND SURVIVAL AT 6 MONTHS AND 1 YEAR

| | 6months | | | | 1year | | |
|---|---|---|---|---|---|---|---|
| single | total | alive | P-value | single | total | alive | P-value |
| goodkfs | 11 | 10 | 0.002 | goodkfs | 11 | 5 | 0.016 |
| badkfs | 25 | 9 | | badkfs | 22 | 2 | |
| | 6months | | | | 1year | | |
| multiple | total | dead | P-value | multiple | total | dead | P-value |
| goodkfs | 11 | 1 | 0.007 | goodkfs | 6 | 2 | 0.005 |
| badkfs | 30 | 16 | | badkfs | 29 | 25 | |

## TABLE-28. TIME INTERVAL BETWEEN PRIMARY AND SECONDARY AND SURVIVAL

| goodkfs | alive | dead | p-value | badkfs | alive | dead | p-value |
|---|---|---|---|---|---|---|---|
| simultaneous | 6 | 7 | 0.002 | simultaneous | 7 | 39 | 0.32 |
| >6months | 7 | 2 | | >6months | 2 | 8 | |

TABLE-29.EDEMA AND SURVIVAL

| | KFS - Good | | KFS - Bad | | P-value |
|---|---|---|---|---|---|
| | Alive | Death | Alive | Death | |
| NO | 3 | 1 | 3 | 5 | 0.221 |
| Severe | 0 | 1 | 3 | 9 | 0.118 |
| | p-value | 0.002 | p-value | 0.059 | |

**NUMBER OF METASTASES AND SURVIVAL:**

Single or multiple metastases was not significantly affecting outcome independently. Performance score was predicting overall survival in multiple metastases patients but not in single metastasis patients(Table-26). Whereas performance score was significantly predicting survival at 6months and 1year in patients with both single and multiple metastases(Table-27).

**TIME INTERVAL BETWEEN PRIMARY AND METASTASES:**

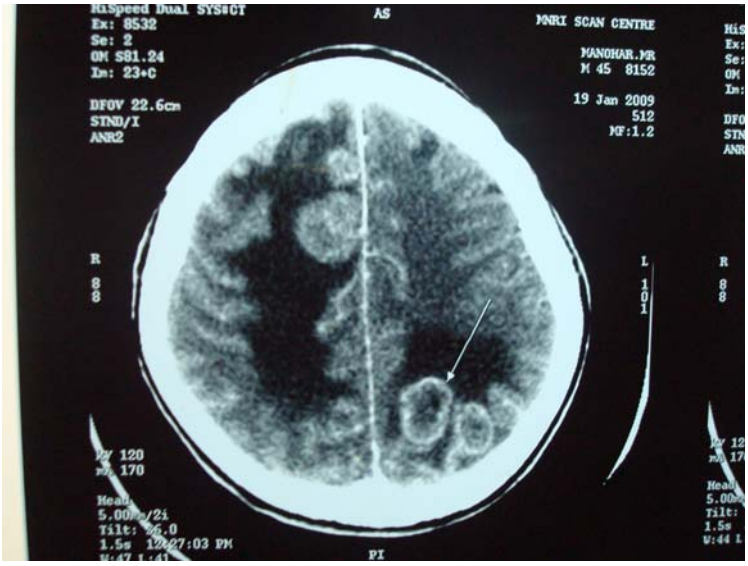
In this study, patients with simultaneous diagnosis of primary and secondary had worse outcome than in patient groups with time interval between primary and secondary was more than 6months. This difference in survival was observed in only good performance score patients and not in patients with bad performance score(Table-28).

**EDEMA AND SURVIVAL ;**

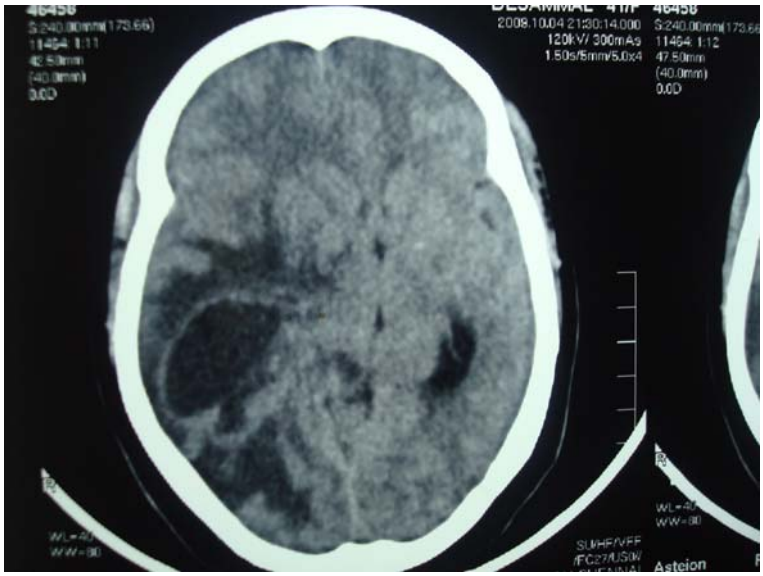
When edema was minimal in imaging, patients had better survival when compared with patients with image showing severe edema . This difference in survival was observation in patients with good performance score and not in patients with bad performance score (Table-29).

Analyzing the factors affecting survival, age less than 40 , good Karnofsky performance status, breast primary were associated with good survival. Age greater than 69, poor performance status, lung primary were associated with poor survival.Treatment modality did not affect outcome independent of performance status. But surgery combined with WBRT had better survival than RT alone in poor performance status patients

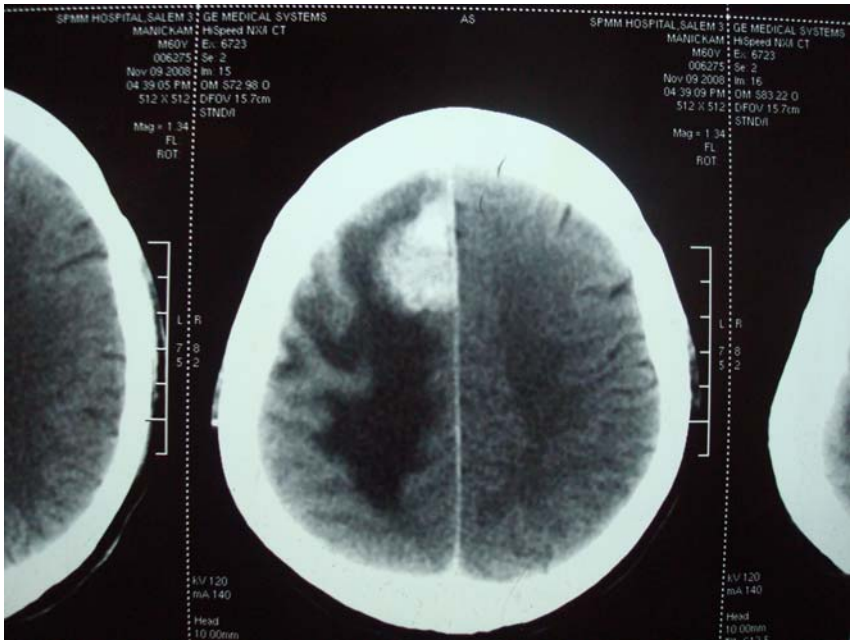
PICTURE-1-RING LESION



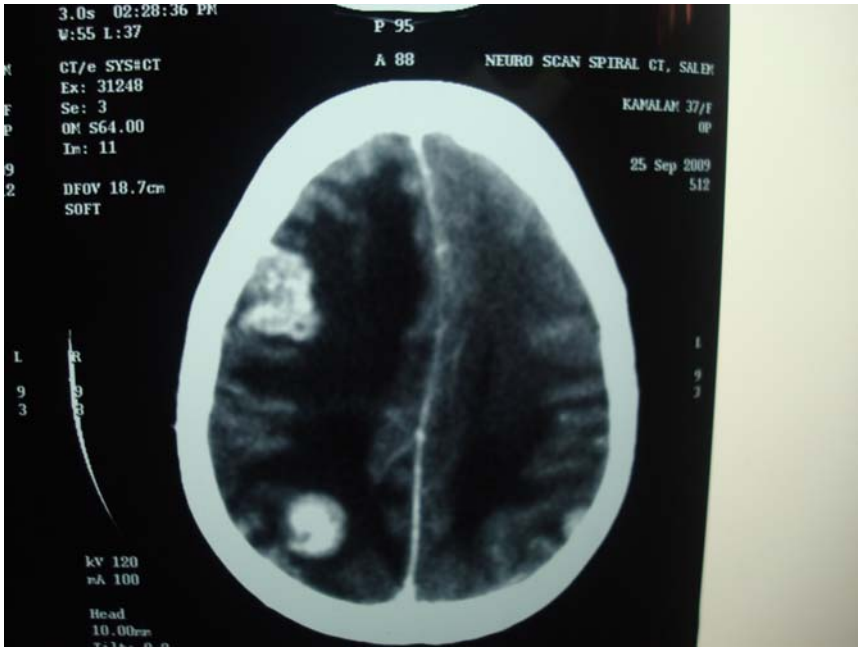

PICTURE-2-CYSTIC METASTASIS



PICTURE-3-HEMORRAGHIC METASTASIS




PICTURE-4-INTENSE CONTRAST ENHANCEMENT



# DISCUSSION :

## AGE

Majority of metastatic brain tumours were in the age group 40 to 69. This is similar to that described in literature . The age distribution is almost similar to the metropolitan Detroit cancer surveillance system[5] .

## SEX

There were 54 male and 48 female patients with a male:female ratio of 1.12:1. Females out-numbered males in less than 40 age group with male:female ratio 1:4. There is not much difference in sex distribution similar to previous studies[14,18] .

## CLINICAL FEATURES:

The average symptom duration before presentation is 10.4 weeks with some cases presenting as early as 1 week to some cases presenting as delayed as one year. This is in concordance with previous studies where the average time interval between the diagnosis of primary cancer and brain metastases is 4 months[18] . Similar to what is described in literature, headache is the most common symptom followed by motor deficit and seizures in that order[14] . Clinical evidence of Cerebellar involvement was present in only 46% cases with radiological evidence of cerebellar involvement. The clinical presentation depends on the location of

intracerebral metastasis. The other clinical features (8.8%) include memory disturbances, speech disturbances, disturbed orientation and lower cranial nerve palsy. There was not much difference between what is observed in this study and literature .

**SOURCE OF PRIMARY:**

The most common source of primary is lung cancer, followed by unknown primary and breast cancer. Lung is the most common source of primary (42%) overall and also in both sexes. It is the most common primary in all age groups except less than 40, where breast is the common primary. In the metropolitan Detroit cancer surveillance system study[5] , breast is the most common primary in females. But in our study even in females lung is the most common source of primary. Melanoma though the 2nd common source of metastasis in western literature[5], is rare in this study. About 60% of breast metastasis incidence, occurred in the less than 40 age group.

Among lung primary, 40% of the cases were small cell carcinoma. Similarly it was observed in previous studies that, small cell carcinomas, which are only 20% of all lung cancers, account for 50% of brain metastases[22].. Infiltrating ductal

carcinoma is the only breast primary producing intracerebral metastases in this study.

**NUMBER OF METASTASIS :**

In this study the incidence of single and multiple metastases is almost similar overall (49:53) and also in lung and breast primary. In unknown primary multiple metastases is common than single metastasis(60.8%). Metastatic disease from the breast, thyroid, renal cells, and colon are more commonly found as a single metastatic lesion, whereas metastatic disease from lung cancer, melanoma and cancers of unknown primary are more commonly found to be multiple lesions in some studies[22] . This is not observed in this study except in unknown primary where multiple metastases is common.

**IMAGING APPEARANCE** :

Majority of brain metastasis (50%) were ring enhancing lesions(picture-1). Cystic appearance that is common in adenocarcinoma secondaries, colon cancer, renal tumours as described in literature[11] is not observed in this study. Cystic appearance was present in lung, renal and unknown primary and they accounted to only 8 cases(picture-2). Hemorrhagic appearance was observed in melanoma and

choriocarcinoma secondaries (picture-3) as described in literature, but the total number is small to suggest a statistical significance.

Majority of lesions exhibited heterogenous and moderate contrast enhancement. Intense homogenous contrast enhancement is seen in 15% only (picture-4) and does not show any source specificity.

In most of the cases of brain metastasis there was only mild to moderate edema. Severe or disproportionate edema was present in only 13.7% cases, whereas in previous studies it was found that cerebral metastases had disproportionate edema[28] . Cerebral Edema in imaging is also not specific to any source of primary.

**SITE OF METASTASIS :**

The most common location is frontal followed by parietal, cerebellum, occipital and temporal. The other location include internal capsule(3), thalamus(3), brainstem(1) and basal ganglia(8). The hemispheric involvement was almost similar with almost equal cases involving the right hemisphere, left hemisphere or both hemispheres. The site of intracerebral metastases is similar to described by Schaefer.et.al . Posterior fossa was involved in 33% of breast primary and 39% of unknown primary and in 20.5% of lung primary. In literature renal,

gastrointestinal, and pelvic cancer tend to metastasize to the cerebellum, whereas breast cancer is more commonly found in the posterior pituitary[11] . In this study renal , GIT, pelvic cancer metastasize to cerebellum in 45%, but the total number of the above primaries are less to be statistically significant. There was no case of metastasis to the pituitary.

**FACTORS AFFECTING SURVIVAL:**

**SYSTEMIC DISEASE;**

In patients with systemic tumour activity in addition to brain metastasis as evidenced by imaging 28% were alive and in the patients with no evidence of systemic disease 29% alive. Systemic tumour activity is not associated with KPS in predicting survival and not an independent factor for survival . This is in contradiction to the RTOG trial were uncontrolled systemic disease was an independent factor affecting survival. In this study systemic tumour activity was determined only by imaging like CT or MRI. PET scan , radioiodine scan , tumour marker study were not done due to unavailability and extra cost . Considering that, when these investigations were performed , as in the RTOG trial ,then the actual incidence of systemic tumour activity might have changed .

**SOURCE OF METASTASIS:**

Breast primary has 58.3% survival rate and performance status is not significantly associated with breast primary in predicting overall survival and survival at 3months and at 6months. Breast primary patients irrespective of their performance status had a 100% 3monthsand 6 months survival rate. Similar findings was observed by Sperduto.et.al in their multi-institutional analysis of 4,259 patients.

Lung primary has 24.3% survival rate and performance status is not significantly associated with lung primary in predicting overall survival and survival at 3 months and 6 months.Unknown primary has 23.8%survival rate and perforamance status significantly predicts overall survival and survival at 3months and 6months in metastatic disease with unknown primary. Unknown primary being an individual good prodnostic factor as described by Sperduto.et.al is not observed in this study [30] .

Lymphoma patients had good overall survival and also patients with GIT primary, but the total number of cases, in these groups is less to be statistically significant.The average survival in weeks for lung, breast, unknown primary are 21, 52.6 and 28 weeks respectively.

**PERFORMANCE STATUS**:

Performance status is determined commonly by the Karnofsky's performance score . The other scoring systems like the RPA also predict the overall survival. Most of the patients had KPS of either 60 or 70. 81% patients had performance score between 40 and 70. Survival duration is directly proportional to the performance score.

The Karnofsky performance status did not predict survival overall, this is because the follow up duration varied between patients in the same Karnofsky score. But the performance score significantly predicted survival at 3months , 6months and 1 year and an independent factor for survival as described inprevious studies.

**TREATMENT MODALITY :**

The survival of patients with bad KPS was higher when craniotomy was combined with WBRT than craniotomy alone. But this difference was not statistically significant. The survival of patients in bad KPS score treated by WBRT combined with craniotomy had better survival significantly than WBRT alone . Treatment modality was not determining the outcome in patients with good performance status. This finding is similar to that I literature were patients treated

with surgery and WBRT had significantly longer median survival than those who received WBRT alone[20] . Similarly the combination of surgical resection followed by WBRT is a more effective treatment for local control of metastatic brain disease compared with surgery or radiotherapy alone[20] .

**AGE AND SURVIVAL**:

Performance status was significantly predicting survival in the 40-69 age group . In age group less than 40 and above 69 , age itself was a predictive factor for survival than performance status.

**NUMBER OF METASTASIS AND SURVIVAL:**

Single or multiple metastases was not significantly affecting outcome independent of performance status. Performance score was predicting survival significantly at 6months and 1year in both single and multiple metastases. This is contrary to some studies where multiple metastases was associated with poor outcome independent of the performance status[29,30] .

**TIME INTERVAL BETWEEN PRIMARY AND SECONDARY:**

There was significant difference between patients, with simultaneous diagnosis of primary and secondary group having worse outcome than patients in

whom the interval between primary and secondary was more than 6months. This difference is observed in only good performance score patients and not in patients with bad performance score.

**EDEMA AND SURVIVAL ;**

When cerebral edema was minimal in imaging patients had better survival when compared with severe edema . This observation is for patients with good KPS and in patients with bad performance status the edema factor was not contributing to overall survival. Thus in good performance score patients factors like cerebral edema in imaging and time interval between primary to secondary diagnosis were having an effect on the overall survival. Whereas in patients with bad performance score, performance status was the better predictor of overall survival.

Thus when analyzing the factors affecting survival, age less than 40, good Karnofsky performance status, breast primary were associated with good survival. Age greater than 69, poor performance status, lung primary were associated with poor survival. Presence of Systemic disease was not affecting the outcome significantly, so does the number of metastases. Karnofsky score was a better predictor of survival individually in age 40-69, unknown primary, single or

multiple metastases. Treatment modality did not affect outcome independent of performance status. But surgery and RT had better survival than RT alone in poor performance status patients.

Edema in imaging and time interval between primary and secondary carry significance only when patients are in good performance score. When patient is moribund, performance score is the more significant factor in predicting survival.

Certain investigations like PET scan, bone scan, radio iodine thyroid scan, tumour markers were not done due to non availability and additional cost. So the actual incidence of systemic tumour activity could be more than reported in this study. Though the presence of multiple metastases was detected in CT brain itself in most of the cases and in only a few cases MRI picked up additional lesions in patients with single metastasis, MRI brain was not done routinely in all patients because of additional cost. . Though streotactic radiosurgery with WBRT has good survival and local control rates, as reported in some studies, SRS was not performed in this study because of non availability.

## CONCLUSION :

In this study of 102 patients with brain metastases, the following conclusions were derived

1. Metastatic disease is common in 40-69 age group.

2. It has equal male female distribution, except in less than 40 age group, in which it is common in females.

3. Headache is the most common symptom followed by motor deficit. Clinical evidence is seen in less than 50% cases with actual incidence of cerebellar involvement.

4. Lung is the most common source of primary in both sexes and in all age groups except in less than 40 age.

5. Breast is the most common source of primary in less than 40 age group.

6. Majority of brain metastases are ring enhancing with moderate edema. Cystic or hemorrhagic appearance is less common and doesnot show disease specificity.

7. Frontal lobe is the most common site of metastases, with both hemispheres equally involved. Site of intracranial metastases is not disease specific.

8. The incidence of single or multiple metastases is almost equal overall and with regard to the source of primary.

9. Age less than 40, good Karnofsky performance status, breast primary were associated with good outcome

10. Age greater than 69, poor performance status, lung primary were associated with poor outcome.

11. Presence of Systemic disease is not an independent factor for survival, so does the number of metastases.

12. In age 40-69, unknown primary, single or multiple metastases, Karnofsky score was a better predictor of survival.

13. Treatment modality did not affect outcome independent of performance status. But surgery and RT had better survival than RT alone in poor performance status patients.

14. Edema in imaging and time interval between primary and secondary significantly affected outcome only when patients are in good performance score. When patient is moribund, performance score is the most significant factor in predicting survival.

# APPENDIX-3

ETHICAL COMMITTEE CERTIFICATE

26

INSTITUTIONAL ETHICAL COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-600 003

Telephone 25363970
Fax 044 2535115
Dated : 12.05.2010

L.Dis.No.14597/ME5/Ethics Dean/MMC/2010

Title of the work : "A Study of Profile of Metastatic Brain tumours."

Principal Investigator : Dr. K. Madhusuthan.
Designation : PG in Neuro Surgery
Department : Madras Medical College & GGH, Ch-3.

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 12th May 2010 at 2.p.m in Pharmacology Seminar Hall, Madras Medical College, Chennai -3

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
4. You should not deviate form the area of the work for which you applied for ethical clearance.
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulation of the institution(s).
7. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

SECRETARY
IEC, MMC,CHENNAI

CHAIRMAN
IEC,MMC,CHENNAI

DEAN
MADRAS MEDICAL COLLEGE,
CHENNAI -3

# APPENDIX-4

CONSENT FORM IN TAMIL

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு :

மூளைக்குப் பரவிய புற்றுநோய் பற்றிய நோயறிதல்

நரம்பியல் அறுவை சிகிச்சை துறை
சென்னை மருத்துவ கல்லூரி

பங்கு பெறுபவரின் பெயர் :

பங்கு பெறுபவரின் வயது :

பங்கு பெறுபவரின் எண் :

பங்கு பெறுபவர் இதனை ( √ ) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது என்னுடைய சந்தேகங்களைக் கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது என அறிந்து கொண்டேன்.

நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகிக் கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்கு பெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன்.

இந்த ஆய்வின் மூலம் கிடைக்கும் நகவலையோ, முடிவையோ பயன்படுத்திக் கொள்ள மறுக்கமாட்டேன்.

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் ---------- இடம் ---------- தேதி ----------
பங்கேற்பவரின் பெயர் மற்றும் விலாசம் :
சாட்சியாளரின் கையொப்பம் :

இடம் : ---------- தேதி : ----------

சாட்சியாளரின் பெயர் மற்றும் விலாசம் :
ஆய்வாளரின் கையொப்பம் :

இடம் : ---------- தேதி :----------

ஆய்வாளரின் பெயர் :----------

30/04

Professor of Neurosurgery
Madras Medical College;
Madras - 3.

Professor of Neurosurgery
Madras Medical College;
Madras - 3.

# APPENDIX-1

## A STUDY OF PROFILE OF METASTATIC BRAIN TUMOURS

NAME: IP NUMBER:

AGE: SEX: MIN NUMBER:

Address: phone no:

CLINICAL FEATURES:

HEADACHE: (y/n)------ DURATION----------

MOTOR :(Y/N)------ DURATION----------

SEIZURES :(Y/N)------ DURATION----------

VISION :(Y/N)------ DURATION----------

CEREBELLAR(Y/N)------- DURATION----------

OTHERS :(Y/N)------ DURATION----------

IMAGING :

| | SINGLE/ MULTIPLE | TYPE OF METASTASIS | PLAIN | CONTRAST | ENHANCEMENT | EDEMA | OTHERS |
|---|---|---|---|---|---|---|---|
| CT | | | | | | | |
| MRI | | | | | | | |

INVESTIGATION:

CT CHEST/CT ABDOMEN:

USG ABDOMEN: OTHERS:

USG BREAST:

TREATMENT;

PRIMARY—:----------

SECONDARY:----------

STEREOTACTIC SURGERY:----------

WBRT :----------

CHEMOTHERAPY:----------

FOLLOW UP :----------

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